Phase Behavior of Biodegradable Polymers in Dimethyl Ether and Dimethyl Ether + Carbon Dioxide

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Phase behavior data are presented for biodegradable polymers in high-pressure dimethyl ether (DME) and in supercritical mixtures of DME and carbon dioxide (CO_2). The cloud point curves of poly(D,L-lactide) (MW = 30000) in DME were measured at polymer concentrations up to ~15 mass % and at temperatures to 373.15 K and pressures to 14 MPa using a variable-volume view cell apparatus. This system exhibited the characteristics of a lower critical solution temperature phase behavior and showed the pressure–polymer concentration isotherms with the maximum cloud point pressure at the polymer concentration of ~5 mass %. The cloud point pressure increased with increasing molecular weight of the poly(D,L-lactide). For poly(D,L-lactide-*co*-glycolide) copolymers in DME, decreasing the D,L-lactide content in the copolymer caused the single-phase region to shrink and changed the cloud point curve from a lower critical solution temperature behavior to an upper critical solution temperature behavior. The cloud points of poly(D,L-lactide) in the solvent mixtures of DME and CO_2 were measured at various CO_2 compositions up to ~73 mass % (on a polymer-free basis) and at temperatures up to ~373.15 K. As the CO_2 composition in the mixed solvent increased, the cloud point pressure at a fixed temperature increased significantly. Addition of CO_2 to DME caused a lowering of the dissolving power of the mixed solvent due to the decrease of the solvent polarity.

Introduction

Supercritical fluid (SCF) solvents are an attractive alternative to incompressible organic liquid solvents because they can have liquidlike dissolving power while exhibiting transport properties of a gas.[1] They have been used in a variety of polymer processes such as extractions and separations, fractionations, and reactions. Particularly, SCF technology has recently gained great attention in the particle formation of biodegradable polymers, which can be used as controlled drug delivery systems of bioactive agents and drugs in pharmaceutical industries.[2–4] In the production of the polymer particles it is important to know the location of the phase boundaries for polymer–solvent mixtures.

The selection of SCF solvents to dissolve polymers is often challenging for processing applications because it is difficult to find a good SCF solvent that will dissolve the polymer at relatively moderate conditions. Carbon dioxide (CO_2) is the favorite solvent in SCF processes because it has a relatively low critical temperature and pressure and because it is inexpensive, nonflammable, nontoxic, and readily available. However, it is not a good solvent for dissolving polar biodegradable polymers, and thus it has been used as an antisolvent when polymer particles have been formed using SCF processes such as a supercritical antisolvent precipitation method.[5,6] On the other hand, polar solvents such as dichloromethane, chlorodifluoro-

methane, and hydrofluorocarbons have been known to be good solvents for the biodegradable polymers. Lee et al.[7,8] observed that poly(L-lactide), a biodegradable polymer, was insoluble in nonpolar CO_2 but was readily soluble in polar chlorodifluoromethane. They also reported the phase behavior of poly(L-lactide) in the supercritical mixtures of chlorodifluoromethane and CO_2.

Dimethyl ether (DME) has also been used to dissolve polar polymers. Lee and McHugh[9] and Hasch et al.[10] reported the phase behavior of poly(ethylene-*co*-methacrylic acid) and poly(ethylene-*co*-methyl acrylate) copolymers in DME. In this work we tested the possibility of dissolving biodegradable polymers using DME as a solvent. The location of the phase boundaries for biodegradable polymer–DME mixtures was determined through cloud point experiments. The cloud point pressures were measured by using a high-pressure variable-volume view cell apparatus. The cloud points of poly(D,L-lactide) in DME were characterized as functions of pressure, temperature, polymer concentration, and polymer molecular weight. Cloud points were measured for poly(D,L-lactide-*co*-glycolide) copolymers with different D,L-lactide contents in DME. Finally, the phase behavior for poly(D,L-lactide) in supercritical mixtures of DME and CO_2 was investigated as a function of CO_2 composition in the mixed solvent. The phase behavior data produced in this work would be useful for establishing operating conditions in the particle formation of biodegradable polymers by the supercritical antisolvent precipitation process that utilizes DME as a solvent and CO_2 as an antisolvent.

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Experimental Section

Materials. The biodegradable polymers used in this study were poly(D,L-lactide) (D,L-PLA) and poly(D,L-lactide-*co*-glycolide) (D,L-PLG). The D,L-PLAs (Resomer R104, MW = 2000; Resomer R203, MW = 30000) were purchased from Boehringer Ingelheim Chemicals, Inc. (Ingelheim, Germany). The D,L-PLG copolymers have four different average D,L-lactide/glycolide mass ratios of 90:10 (MW = 5000), 80:20 (MW = 5000), 70:30 (MW = 10000), and 55:45 (MW = 14500). The 55:45 D,L-PLG (Resomer RG502) was purchased from Boehringer Ingelheim Chemicals, Inc., and all of the other D,L-PLGs were from Polysciences, Inc. (Warrington, PA). The polymer molecular weights described above, provided by the suppliers, are the viscosity-average molecular weights derived from the intrinsic viscosity and Mark–Houwink equation. DME of 99+% purity was obtained from Aldrich Chemical Co. (Milwaukee, WI) and CO_2 of 99.99% purity from Myung-Sin General Gas Co. (Yangsan, Kyungnam, Korea). They were used as received without further purification.

Apparatus and Procedure. The cloud point behavior of the biodegradable polymers in pure DME and in the mixtures of DME and CO_2 was measured using a high-pressure apparatus equipped with a variable-volume view cell. A main feature of using the variable-volume cell apparatus is that the concentration of the system is kept constant during the experiment. A detailed description of the experimental apparatus and procedure is given in our previous publications.[7,8] The apparatus consists of a view cell equipped with a sapphire window and a movable piston, a pressure generator (High-Pressure Equipment Co., model 50-6-15), a borescope (Olympus, model R080-044-000-50), a video monitor, and a magnetic stirring system. The view cell has dimensions of 16 mm i.d. by 70 mm o.d. and an internal working volume of ~31 cm³. The system pressure is measured using a high-precision pressure gauge (Dresser Heise, model CC-12-G-A-02B, ±0.05 MPa accuracy, ±0.01 MPa resolution) and a piezoresistive pressure transmitter (Keller Druckmesstechnik, type PA-25HTC/8585-1000). The system temperature is measured to within ±0.1 °C by an RTD (Pt-100 Ω) probe inserted into the cell.

The experiment for measuring a cloud point was performed by the following procedure. To remove any entrapped air present in the cell, the cell was purged with enough solvent gas used in the experiment. A certain amount of the polymer was loaded into the cell. The amount of the polymer loaded into the cell was determined using a sensitive balance (AND, model HM-300) measurable to ±0.1 mg. The solvent was charged into the cell using a high-pressure sample cylinder. In the case of both DME and CO_2 being charged, DME was first charged because its vapor pressure was lower than that of CO_2. The composition of each component in the solvent mixture was determined by weighing DME and CO_2 sample cylinders before and after they had been charged into the cell using a balance (Precisa, model 1212 M SCS) with an accuracy of ±1 mg. To minimize the amount of components lost when charging them into the cell, we used a fine and short inlet line (0.03 in. i.d., 10 cm long) and heated it by a heat gun for enough time. The uncertainty in solvent composition measurement was <0.02 mass %.

The solution in the cell was compressed by moving the piston located within the cell using the pressure generator and agitated by the magnetic stirrer until it became a single phase. The cell was then heated to a desired temperature. Once the system reached thermal equilibrium

Table 1. Experimental Data of Cloud Points of D,L-PLA (1) in DME (2)

MW of D,L-PLA	$100w_1{}^a$	T/K	P/MPa
30000	0.57	333.25	1.65
		338.75	3.05
		343.15	4.25
		352.65	6.85
		363.85	9.65
		372.45	11.75
30000	2.91	328.55	2.19
		333.15	3.42
		343.75	6.29
		352.75	8.53
		362.85	11.04
		373.35	13.45
30000	5.00	328.65	2.47
		333.05	3.75
		343.05	6.55
		354.15	9.27
		363.35	11.45
		372.95	13.73
30000	7.99	327.15	1.70
		333.55	3.65
		343.95	6.65
		352.95	8.93
		363.15	11.60
		373.25	13.83
30000	14.67	329.25	1.70
		332.95	2.80
		343.55	5.90
		353.05	8.50
		363.05	11.01
		372.45	13.23
2000	2.97	358.35	4.25
		363.15	5.50
		367.45	6.35
		375.15	8.10

^{a} Mass fraction of D,L-PLA in solution.

and the solution was maintained at a single phase, the pressure was then slowly reduced until the solution became cloudy. Enough time was allowed to ensure thermal equilibrium during the pressure reduction. The pressure was reduced very slowly as the cloud point pressure was approached. At fixed polymer and solvent concentrations and temperature, the cloud point was defined as the pressure at which it was no longer possible to visually observe the stirring bar. For obtaining consistent measurements, every measurement was repeated at least twice at each temperature. Reproducibility of the cloud point pressures was within ±0.2 MPa. The temperature of the system was raised in ~10 K increments, and the above procedure was repeated, thus creating a pressure–temperature (P–T) cloud point curve at fixed polymer and solvent concentrations.

Results and Discussion

The cloud points of D,L-PLA in DME were investigated as functions of pressure, temperature, polymer concentration, and polymer molecular weight. The experimental cloud point data are given in Table 1. Figure 1 shows the P–T isopleths of the cloud points of D,L-PLA (MW = 30000) in DME at various polymer concentrations up to ~15 mass %. The saturation curve of DME, which is obtained from Daubert and Danner,[11] is also shown along with the cloud point data. Above each cloud point is the single-phase region, and below the point is the two-phase region. This system exhibited the characteristics of a typical lower
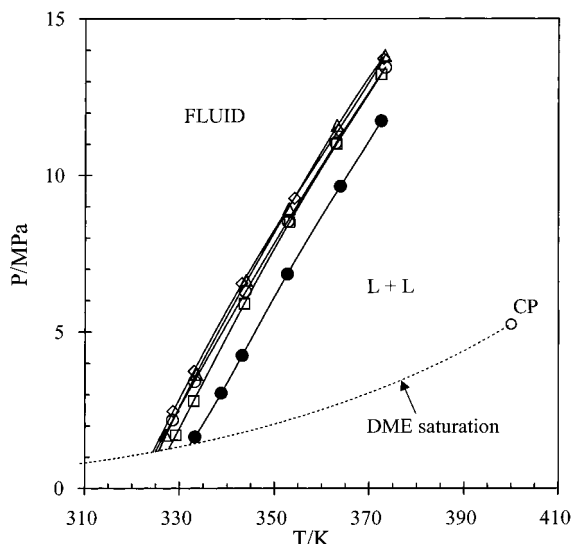
Figure 1. $P-T$ isopleths of cloud points of poly(D,L-lactide) (MW = 30000) in DME at various polymer concentrations: ●, 0.57 mass %; ○, 2.91 mass %; ◇, 5.00 mass %; △, 7.99 mass %; □, 14.67 mass %.

Figure 2. Pressure−polymer concentration isotherms for poly-(D,L-lactide) (MW = 30000) in DME at various temperatures: ●, 333.15 K; ■, 343.15 K; ◆, 353.15 K; ▲, 363.15 K; ○, 373.15 K.

critical solution temperature (LCST) phase behavior. The cloud point pressure was as low as ~14 MPa even at 393.15 K, indicating that DME was a good solvent to dissolve the D,L-PLA. DME has a dipole moment of 1.3 D,[12] and thus it is expected to be capable of dissolving the polar D,L-PLA polymer. The cloud point curves had similar slopes for all of the polymer concentrations. The cloud point curve intersected the DME saturation curve at the lower critical end point (LCEP), at which the fluid- to liquid−liquid-phase transition ended. The fluid- to liquid−vapor-phase transitions occurred on the DME saturation curve at temperatures below the LCEP. The LCEPs for the D,L-PLA (MW = 30000) + DME system were observed around 330 K and 1.2 MPa, as shown in Figure 1.

The $P-T$ isopleths of the cloud points given in Figure 1 were further characterized by drawing a pressure−polymer concentration diagram. The pressure−polymer concentration profile was obtained by fitting the cloud point curves at different polymer concentrations with polynomial equations and then by determining the pressures corresponding to desired temperatures from the curve fits. Figure 2 shows the pressure−polymer concentration isotherms for the D,L-PLA (MW = 30000) + DME system. The pressure necessary to maintain the polymer solution in the single-phase region increased with the temperature. As shown in each isotherm, the maximum cloud point pressure, that is, an upper critical solution pressure, was observed at the polymer concentration of ~5 mass %. Figure 3 shows the effect of the polymer molecular weight on the cloud points for the D,L-PLA + DME system. As the polymer molecular weight increased, the cloud point pressure increased. Increasing the polymer molecular weight reduced the single-phase region.

The cloud point results of D,L-PLG copolymers in DME are given in Table 2 and Figure 4. The D,L-PLG concentration in the solution was kept at (2.98 ± 0.13) mass %. As the D,L-lactide/glycolide mass ratios in the copolymers decreased from 90:10 to 55:45, the cloud point pressures increased at a given temperature. Decreasing the D,L-lactide content in the D,L-PLG caused the single-phase region to shrink and changed the cloud point curve from an LCST behavior to an upper critical solution temperature (UCST) behavior. The cloud point curves for the 70:30 and
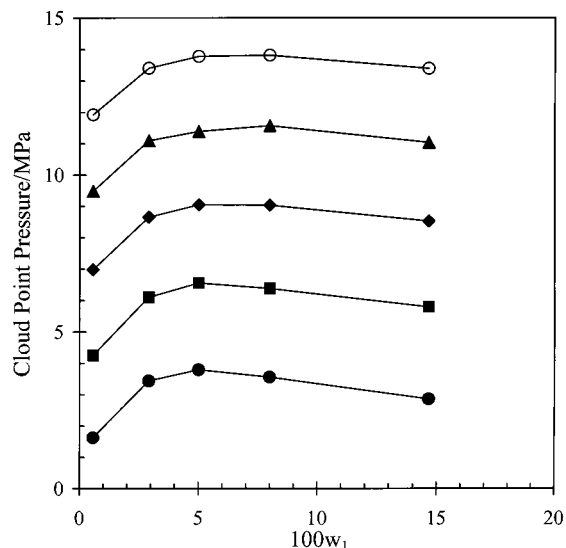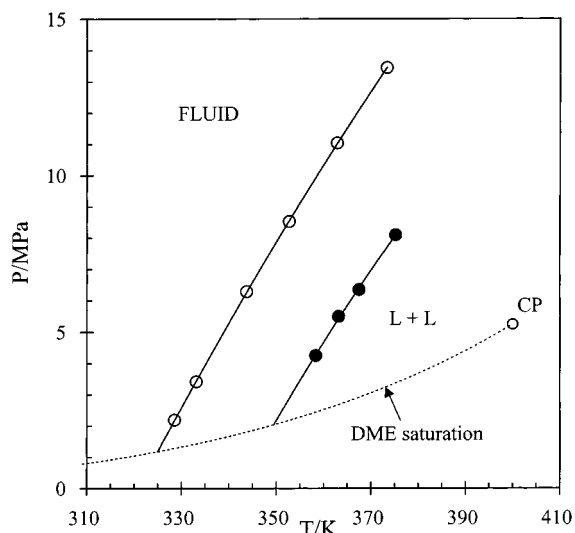

Figure 3. Effect of polymer molecular weight on cloud points of poly(D,L-lactide) in DME: ●, MW = 2000; ○, MW = 30000. Polymer concentrations are 2.97 mass % for poly(D,L-lactide) (MW = 2000) and 2.91 mass % for poly(D,L-lactide) (MW = 30000), respectively.

55:45 D,L-PLGs exhibited the UCST curve where the slope of the curves is negative in the $P-T$ plane.

The phase behavior of D,L-PLA in the solvent mixtures of DME and CO_2 was investigated as a function of solvent composition. The experimental cloud point data are given in Table 3. Figure 5 shows the $P-T$ isopleths of the cloud points of the D,L-PLA (MW = 30000) in the mixed solvents of DME and CO_2 for various CO_2 compositions up to ~73 mass % (on a polymer-free basis). The polymer concentration in the solution was fixed at (4.76 ± 0.28) mass % of total, to eliminate the effect of the polymer concentration on the cloud points. The cloud point curves exhibited the characteristics of an LCST curve for all of the CO_2 compositions. As the CO_2 composition in the solvent increased, the cloud point curve was shifted to higher pressures so that the single-phase region of polymer−solvent miscibility shrunk. Addition of CO_2 to DME caused a lowering of the dissolving power of the mixed solvent.

Table 2. Experimental Data of Cloud Points of D,L-PLG (1) Copolymers in DME (2)

D,L-lactide/glycolide mass ratio in D,L-PLG	MW of D,L-PLG	$100 w_1{}^a$	T/K	P/MPa
90:10	5000	3.14	303.65	8.55
			314.35	11.37
			323.55	13.50
			333.15	15.62
			343.25	17.65
			352.75	19.50
			363.05	21.44
			373.25	23.29
80:20	5000	2.93	303.35	21.65
			312.85	23.55
			323.75	25.10
			333.75	26.50
			343.15	28.00
			353.45	29.75
			363.45	31.25
			373.05	32.65
70:30	10000	2.75	305.15	49.05
			314.15	48.45
			323.75	47.95
			333.65	47.35
			343.25	46.65
			353.25	46.05
			362.95	45.15
			373.45	44.25
55:45	14500	3.09	324.85	61.35
			333.85	58.85
			343.35	56.65
			353.05	55.25
			363.35	53.75
			373.35	52.35

^{a} Mass fraction of D,L-PLG in solution.
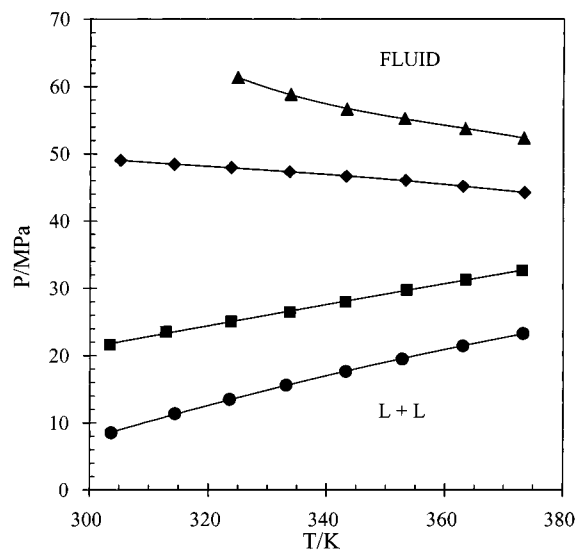
Figure 4. Effect of D,L-lactide content on cloud points of poly-(D,L-lactide-*co*-glycolide) copolymers in DME. D,L-Lactide/glycolide mass ratios in poly(D,L-lactide-*co*-glycolide): ●, 90:10; ■, 80:20; ◆, 70:30; ▲, 55:45.

This can be attributed to the decrease of the solvent polarity by the increase of CO_2 composition in the solvent.

The $P-T$ isopleths of the cloud points given in Figure 5 were further characterized by drawing the cloud point pressures as a function of solvent composition. Figure 6 shows the effect of CO_2 composition in the mixed solvent on the cloud point pressures at several temperatures. It was obtained by fitting the cloud point curves of Figure 5

Table 3. Experimental Data of Cloud Points of D,L-PLA (1) (MW = 30000) in $(1 - w_2)$DME + w_2CO$_2$

$100 w_2{}^a$	$100 w_1{}^b$	T/K	P/MPa
0.00	5.00	328.65	2.47
		333.05	3.75
		343.05	6.55
		354.15	9.27
		363.35	11.45
		372.95	13.73
12.83	5.21	303.45	2.52
		313.95	5.73
		323.15	8.55
		333.55	11.50
		342.85	13.75
		353.55	16.12
		362.75	18.25
		373.35	20.65
21.27	4.39	303.05	8.55
		314.25	11.95
		325.95	15.15
		333.65	17.39
		342.85	19.65
		353.15	21.70
		363.05	23.82
		372.95	25.95
32.80	4.68	303.25	18.70
		313.25	21.35
		323.45	23.99
		333.65	26.42
		342.95	28.80
		353.75	30.82
		362.85	32.35
		372.95	34.28
42.22	4.85	304.55	27.12
		313.05	29.33
		322.95	31.72
		333.85	34.12
		342.95	36.20
		353.45	37.79
		362.75	39.49
		372.75	41.40
49.55	4.56	304.05	33.90
		313.45	35.99
		323.55	38.48
		333.55	40.79
		343.05	42.95
		353.05	44.95
		362.75	46.15
		373.15	47.75
63.10	4.28	303.65	45.95
		313.75	48.95
		323.25	51.35
		333.05	53.75
		343.35	56.25
		353.25	57.75
		363.25	58.65
		373.25	60.25
72.79	5.10	304.15	56.25
		313.25	59.35
		324.55	62.75
		334.15	65.45
		342.95	67.85
		353.05	69.75
		363.45	70.85
		373.35	72.45

^{a} Mass fraction of CO_2 in a mixed solvent of DME + CO_2 on a polymer-free basis. ^{b} D,L-PLA mass fraction of total.

with polynomial equations and then by determining the pressures corresponding to desired temperatures from the curve fits. The correlation coefficients of the curve fits, which expressed the goodness of the fits, were >0.999 for
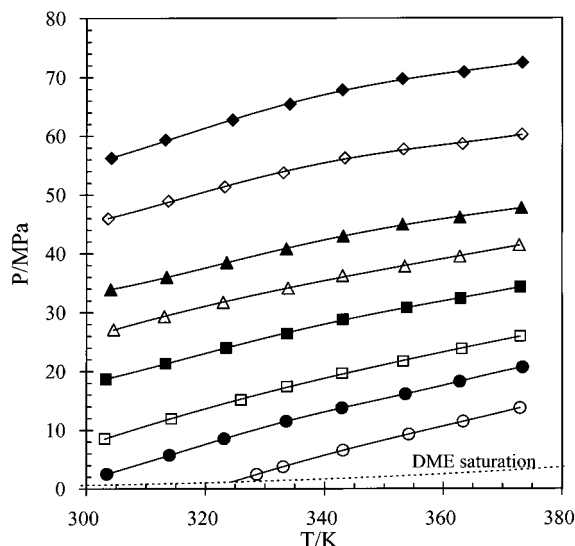
Figure 5. $P-T$ isopleths of cloud points of poly(D,L-lactide) (MW = 30000) in a DME + CO_2 mixed solvent. Compositions of CO_2 in the mixed solvent (on a polymer-free basis): ○, 0.0 mass %; ●, 12.83 mass %; □, 21.27 mass %; ■, 32.80 mass %; △, 42.22 mass %; ▲, 49.55 mass %; ◇, 63.10 mass %; ◆, 72.79 mass %.
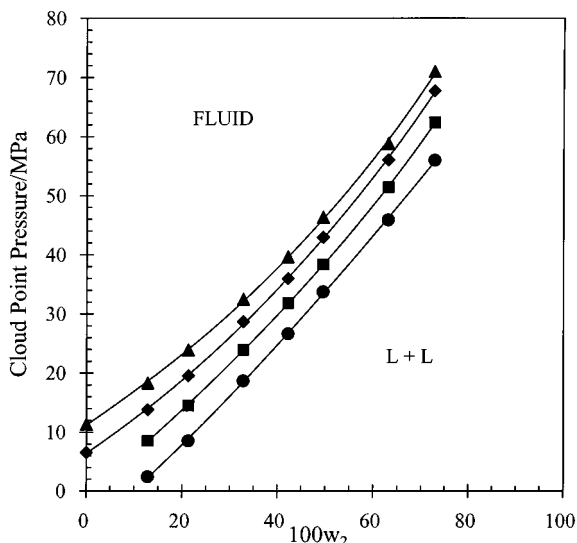

Figure 6. Effect of CO_2 composition (w_2, on a polymer-free basis) in a mixed solvent on cloud point pressures of poly(D,L-lactide) (MW = 30000) at various temperatures: ●, 303.15 K; ■, 323.15 K; ◆, 343.15 K; ▲, 363.15 K.

all cases. The cloud point pressures increased sharply with increasing CO_2 composition in the mixed solvent.

Conclusions

The cloud point experiments indicated LCST phase behavior for D,L-PLA in DME and in DME + CO_2 mixtures.

DME was observed to be a high-quality solvent for the D,L-PLA polymer. The cloud point pressure was relatively insensitive to the D,L-PLA concentration. At a given temperature, the cloud point pressure increased with increasing molecular weight in the D,L-PLA and with decreasing D,L-lactide content in the D,L-PLG copolymers. Addition of CO_2 to the D,L-PLA + DME solution lowered the dissolving power of the mixed solvent due to the decrease of the solvent polarity and reduced the area of miscibility by shifting the cloud point curve to lower temperatures and higher pressures. CO_2 acted as an antisolvent. In practice, this means that polymer solutions can be separated at lower temperatures.

Note Added after ASAP Posting

An incorrect title for Table 3 was inadvertently used for initial Web posting on August 21, 2001. The correct Table 3 title is shown in this posting.

Literature Cited

(1) McHugh, M. A.; Krukonis, V. J. *Supercritical Fluid Extraction, Principles and Practice*, 2nd ed.; Butterworth-Heinemann: Boston, MA, 1994.
(2) Bodmeier, R.; Wang, H.; Dixon, D. J.; Mawson, S.; Johnston, K. P. Polymeric Microspheres Prepared by Spraying into Compressed Carbon Dioxide. *Pharm. Res.* **1995**, *12*, 1211−1217.
(3) Kim, J.-H.; Paxton, T. E.; Tomasko, D. L. Microencapsulation of Naproxen Using Rapid Expansion of Supercritical Solutions. *Biotechnol. Prog.* **1996**, *12*, 650−661.
(4) Benedetti, L.; Bertucco, A.; Pallado, P. Production of Micronic Particles of Biocompatible Polymer Using Supercritical Carbon Dioxide. *Biotechnol. Bioeng.* **1997**, *53*, 232−237.
(5) Reverchon, E. Supercritical Antisolvent Precipitation of Micro- and Nanoparticles. *J. Supercrit. Fluids* **1999**, *15*, 1−21.
(6) Reverchon, E.; Della Porta, G.; De Rosa, I.; Subra, P.; Letourneur, D. Supercritical Antisolvent Micronization of Some Biopolymers. *J. Supercrit. Fluids* **2000**, *18*, 239−245.
(7) Lee, J. M.; Lee, B.-C.; Lee, S.-H. Cloud Points of Biodegradable Polymers in Compressed Liquid and Supercritical Chlorodifluoromethane. *J. Chem. Eng. Data* **2000**, *45*, 851−856.
(8) Lee, J. M.; Lee, B.-C.; Hwang, S.-J. Phase Behavior of Poly(L-lactide) in Supercritical Mixtures of Carbon Dioxide and Chlorodifluoromethane. *J. Chem. Eng. Data* **2000**, *45*, 1162−1166.
(9) Lee, S.-H.; McHugh, M. A. Phase Behavior Studies with Poly-(ethylene-*co*-methacrylic acid) at High Pressure. *Polymer* **1997**, *38*, 1317−1322.
(10) Hasch, B. M.; Lee, S.-H.; McHugh, M. A. Strengths and Limitations of SAFT for Calculating Polar Copolymer−Solvent Phase Behavior. *J. Appl. Polym. Sci.* **1996**, *59*, 1107−1116.
(11) Daubert, T. E.; Danner, R. P. *Physical and Thermodynamic Properties of Pure Compounds: Data Compilation*; Taylor and Francis: New York, extent 1994.
(12) Reid, R. C.; Prausnitz, J. M.; Poling, B. E. *The Properties of Gases and Liquids*, 4th ed.; McGraw-Hill: New York, 1987.

JE010056O